DSHS Grand Rounds

Sept. 16

Assessing Emerging Treatments for Depression

Presenter: Marilyn J. Vaché, MD, PA
Austin TMS Clinic for Depression

Logistics

Registration for free continuing education (CE) hours or certificate of attendance through TRAIN at: https://tx.train.org

Streamlined registration
for individuals not requesting CE hours
or a certificate of attendance

1. webinar: http://www.dshs.state.tx.us/grandrounds/webinar-no-CE.shtm
2. live audience: sign in at the door

For registration questions, please contact Laura Wells, MPH at CE.Service@dshs.state.tx.us

Logistics (cont.)

Slides and recorded webinar available at:
http://www.dshs.state.tx.us/grandrounds

Questions?
There will be a question and answer period at the end of the presentation. Remote sites can send in questions throughout the presentation by using the GoToWebinar chat box or email GrandRounds@dshs.state.tx.us.

For those in the auditorium, please come to the microphone to ask your question.

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Disclosure to the Learner

Requirement of Learner

Participants requesting continuing education contact hours or a certificate of attendance must register in TRAIN, attend the entire session, and complete the online evaluation within two weeks of the presentation.

Commercial Support

This educational activity received no commercial support.

Disclosure of Financial Conflict of Interest

The speaker and planning committee have no relevant financial relationships to disclose.

Off Label Use

There will be no discussion of off-label use during this presentation.

Non-Endorsement Statement

Accredited status does not imply endorsement by Department of State Health Services - Continuing Education Services, Texas Medical Association, or American Nurses Credentialing Center of any commercial products displayed in conjunction with an activity.

Additional Readings

1. Morishita, T., fayad, S. M., higuchi, M., nestor, K. A., & foote, K. D. (2014). deep brain stimulation for treatment-resistant depression: Systematic review of clinical outcomes. *neurotherapeutics*, *11*(3), 475–484. doi:10.1007/s13311-014-0282-1. .

2. Leiknes, K. A., jarosh-von schweder, L., & høie, B. (2012). contemporary use and practice of electroconvulsive therapy worldwide. *brain and behavior*, *2*(3), 283–344. doi:10.1002/brb3.37.

3. Cretaz, E., brunoni, A. R., & lafer, B. (2015). magnetic seizure therapy for unipolar and bipolar depression: A systematic review. *neural plasticity*, *2015*, 521398. doi:10.1155/2015/521398. .

4. Pehrson, A. L., & sanchez, C. (2014). serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction. *CNS spectrums*, *19*(2), 121–133. doi:10.1017/S1092852913000540. .

5. Mahableshwarkar, A. R., jacobsen, P. L., chen, Y., serenko, M., & trivedi, M. H. (2015). A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *psychopharmacology*, *232*(12), 2061–2070. doi:10.1007/s00213-014-3839-0. .

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Introductions

Kirk Cole
DSHS Interim Commissioner is pleased
to introduce our DSHS Grand Rounds speaker.

Marilyn Vaché, MD

Mariyn Vaché, MD is a board-certified psychiatrist and addiction medicine specialist in Austin, Texas.

She interned at Brackenridge and trained in psychiatry and addiction medicine at Stanford University.

Dr. Vaché has a private practice in general adult psychiatry and serves as Medical Director of the Council on Recovery.

Learning Objectives

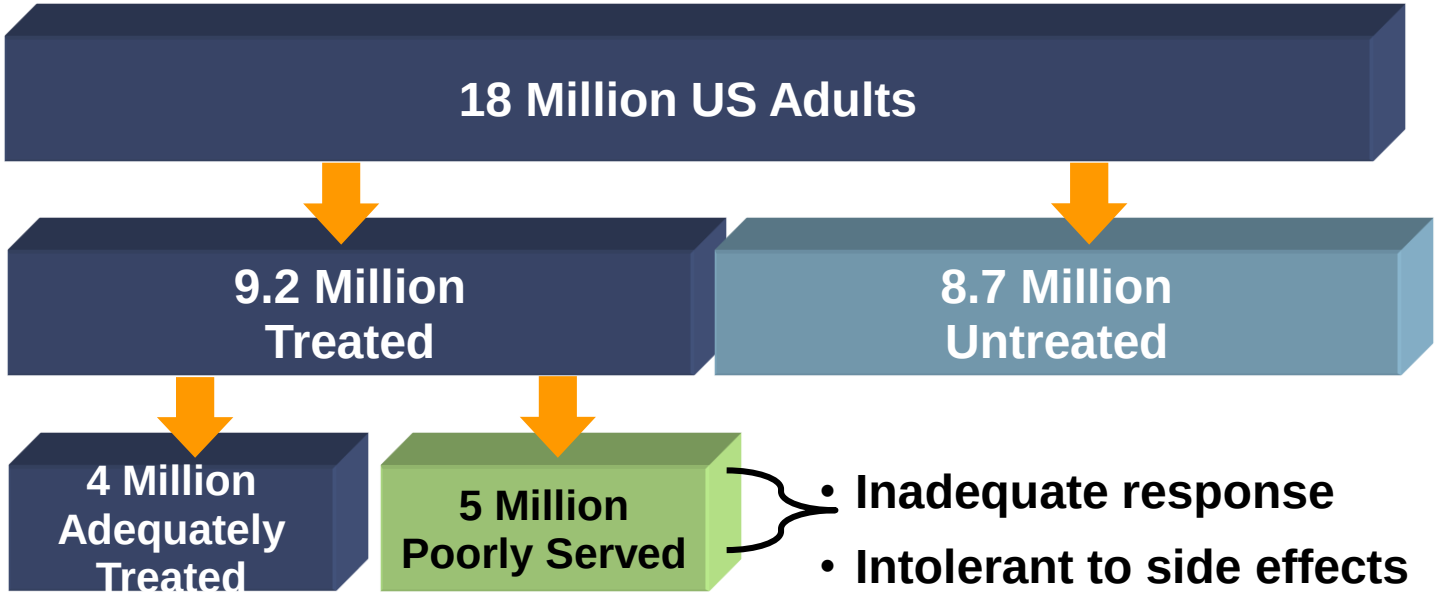
Participants should be able to:

1. Describe the promise and limitation of ketamine as a therapy for depression

2. Describe two common general health conditions related to depression

3. Describe the indications for TMS in major depression

A Significant Percentage of Patients With MDD Remain Poorly Served



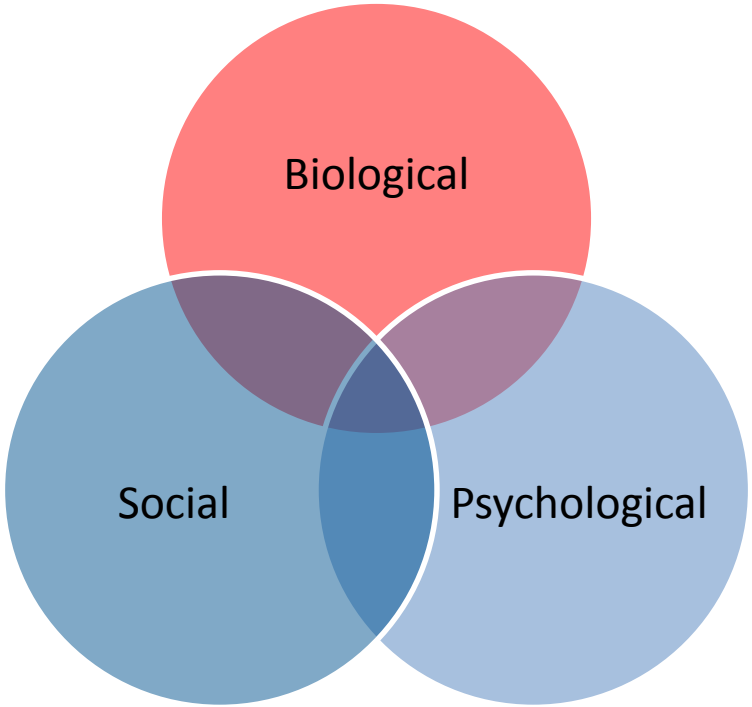
Kessler RC et al. *JAMA*. 2003;289(23):3095-3105.

MDD affects other health conditions

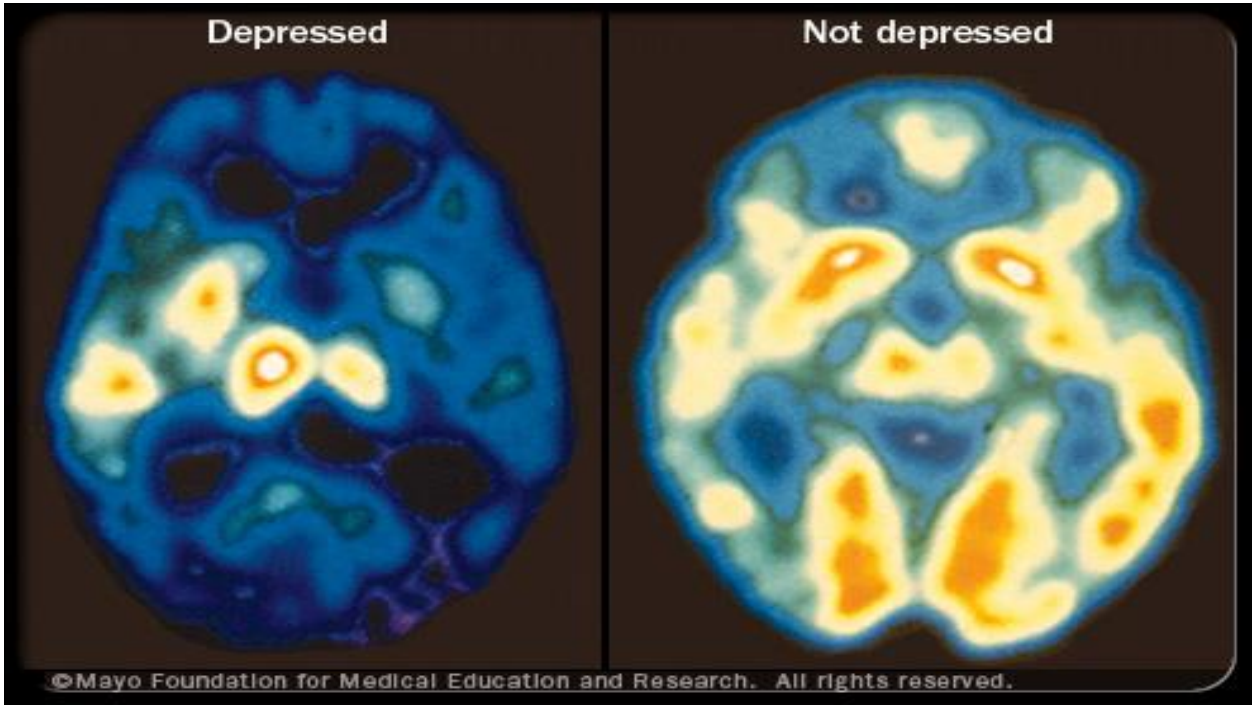
- MDD has been shown to be an independent factor affecting the morbidity and mortality for the following:
  - All cause mortality[1]
  - Acute stroke[2]
  - Diabetes[3]
  - Myocardial infarction[4]
  - Cardiovascular disease[5]
  - Congestive heart failure[6]
  - HIV[7]

1. Murphy, JM, et al *Arch Gen Psychiatry*. 1987. 44(5)473-480; 2. Everson, SA, et. al. *Arch Intern Med.* 1998; 158(10): 1133-1138; 3. Lustman, PT, et.al. *Diabetes Care.* 2000: 23(7): 934-942; 4. Frasure-Smith, N, et. al. *JAMA.* 1993; 270(15): 1819-1825; 5. Penninx, BW, et. al. *Arch Gen Psych*. 2001; 58(3): 221-227. 6. Vaccarino, V, et. al J. *Am Coll Cardiol.* 2001; 38(1): 199-205. 7. Ickovics, JR, et. *JAMA*. 2001: 285(11): 1466-1474.

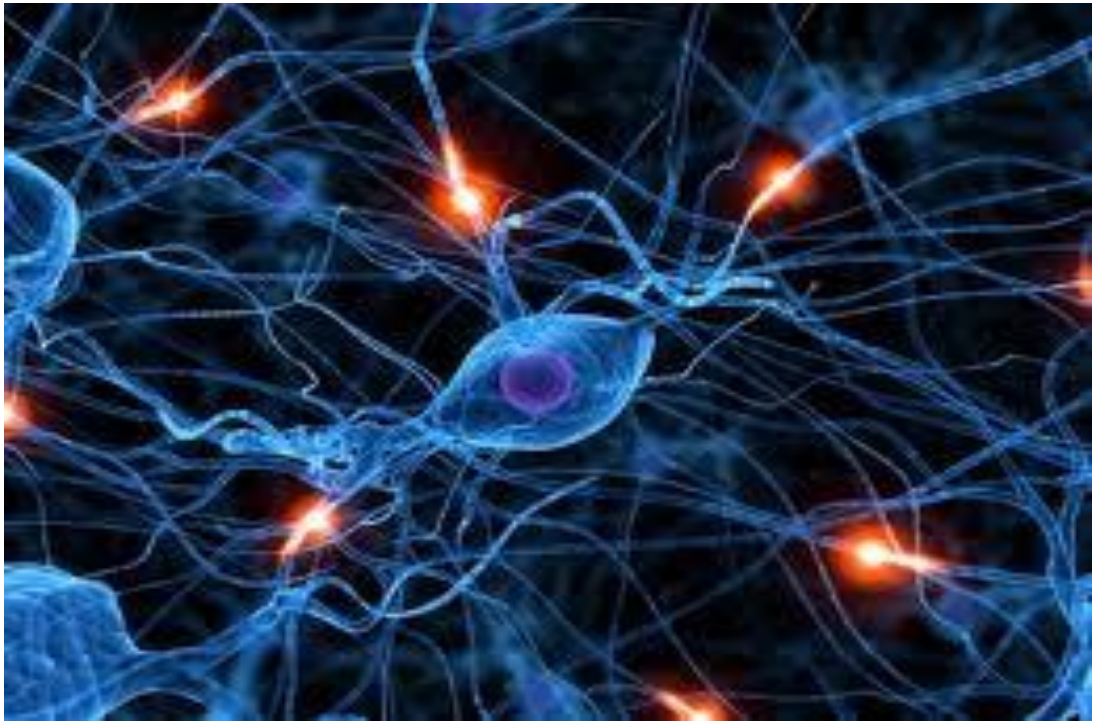
How Can We Treat Depression



Major Depression is a Brain Disease



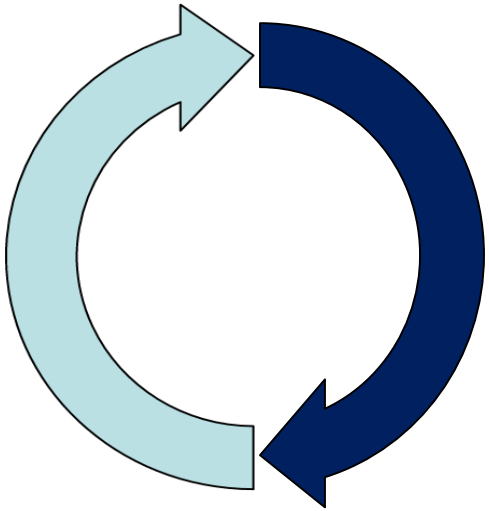
Biology of the Brain - Starts with Neurons



Electrical Impulses

- Think
- Feel
- Remember

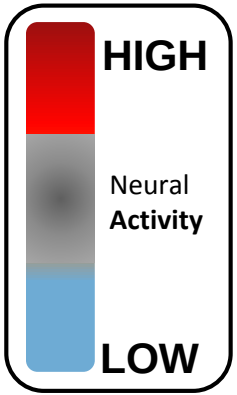
How do the Neurons Communicate?

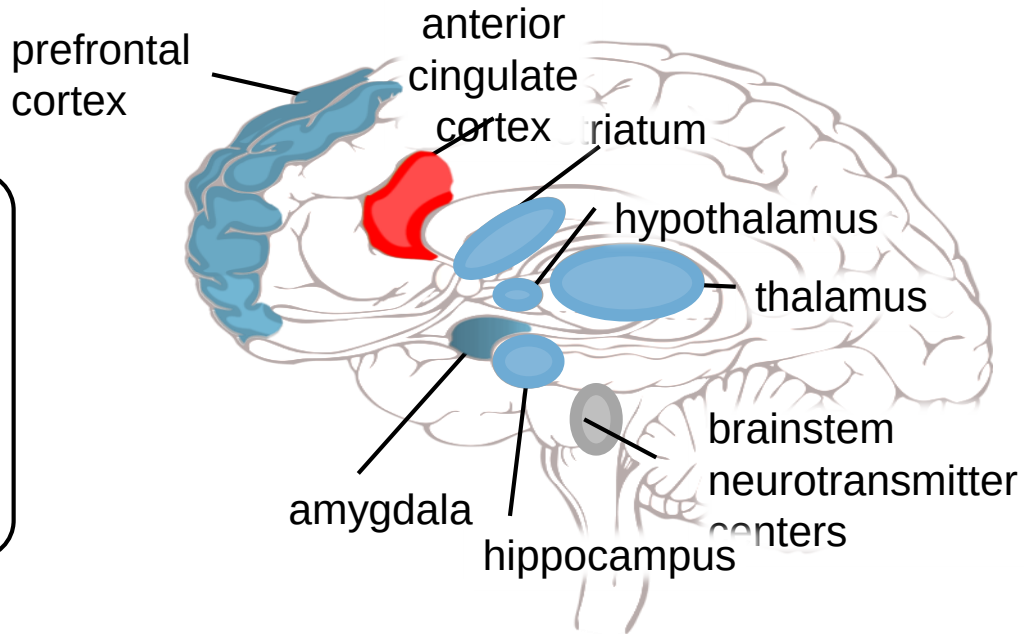


- Chemical Signals
- Electrical Signals

They each cause the other to respond

Major Depressive Disorder





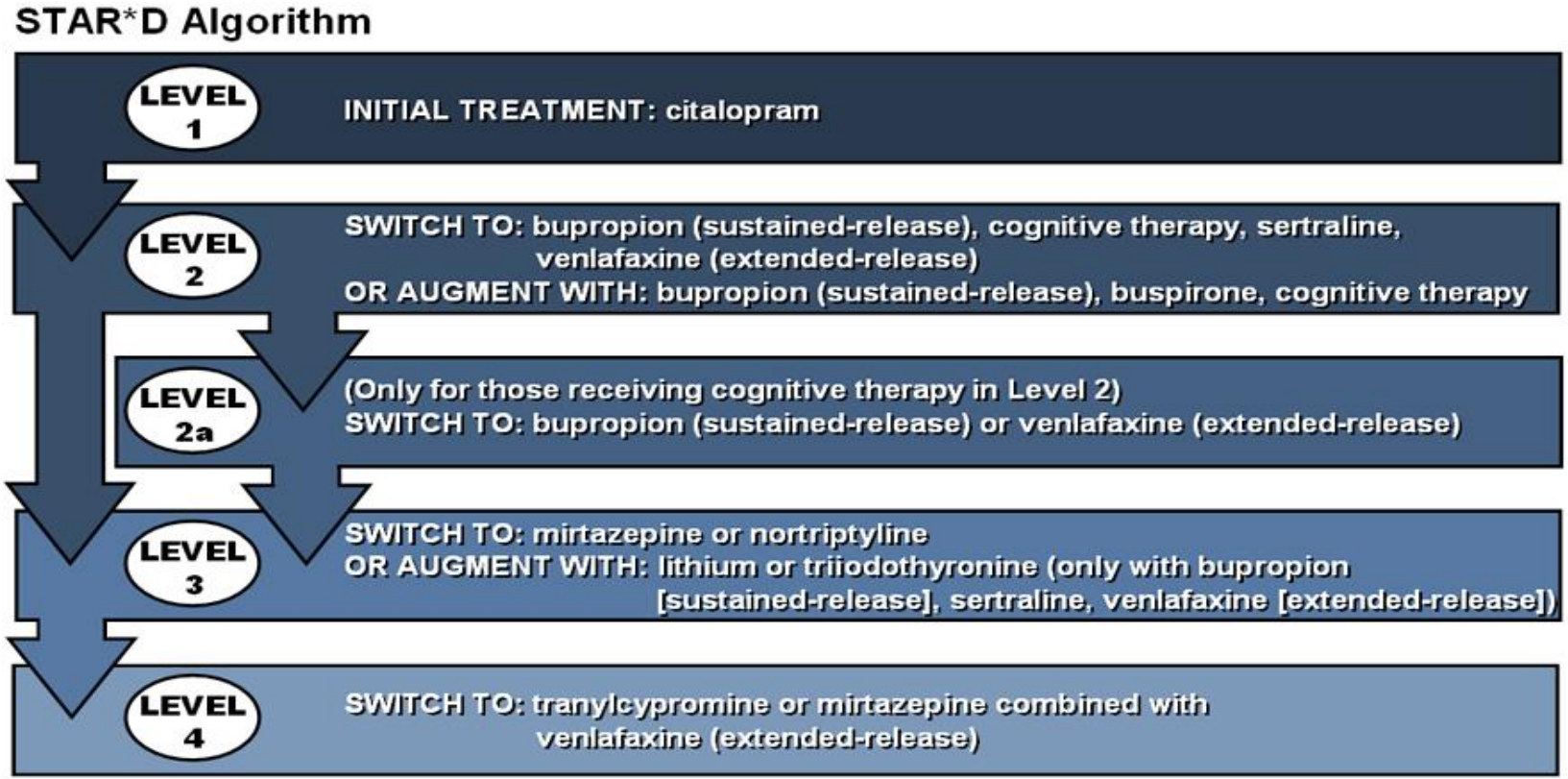
In MDD, some areas of the brain are hypoactive and others are hyperactive.

The Pharmaceutical Paradigm

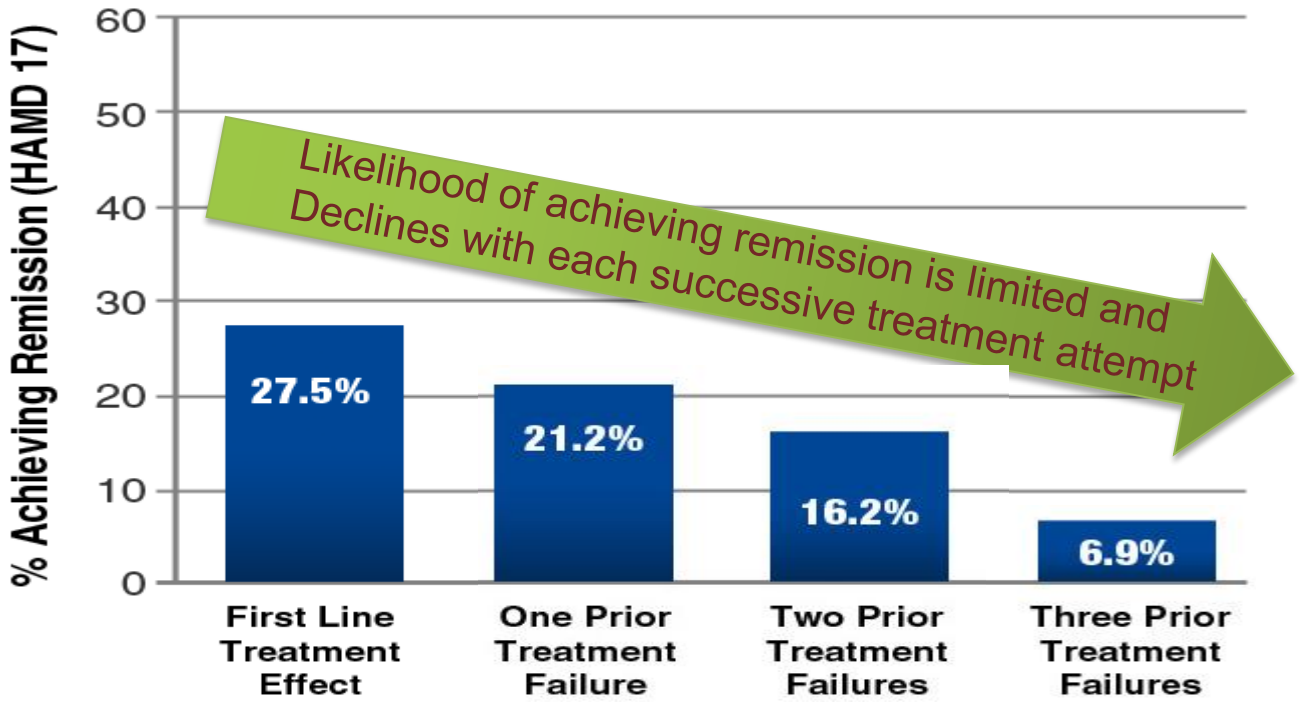
Improve synaptic firing by changing neurotransmitter levels:

- Serotonin (5-HT)
- Norepinephrine (NE)
- Dopamine (DA)
- Glutamate

STAR*D Treatment Algorithm

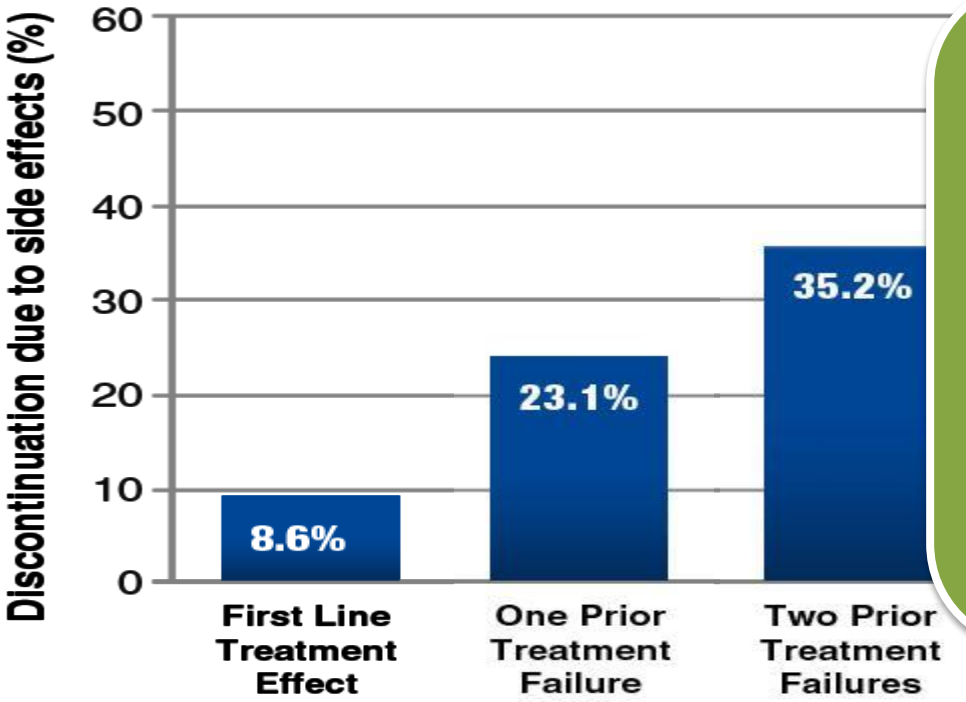


Study demonstrates that medication treatment have limited effectiveness



Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

Study also demonstrates the discontinuing treatment increases with each NEW medication



Systemic Drug Side Effects

- Weight Gain
- Constipation
- Fatigue
- Headache/ Migraine
- Abnormal Ejaculation
- Impotence
- Sweating
- Tremor
- Treatment Discontinuation Side Effects
- Weakness
- Dry Mouth
- Dizziness

Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*; Neuronetics, Inc. (data on file)

The Pharmaceutical Paradigm

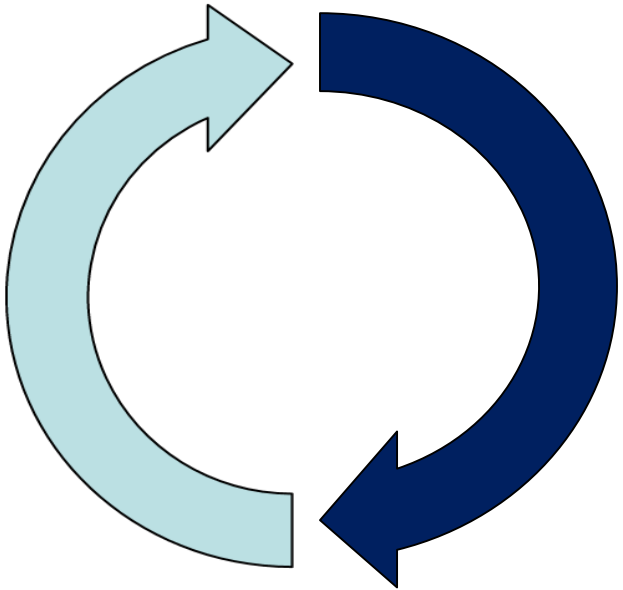
Recent additions:

- Vilazidone **(Viibryd)** – 5-HT reuptake inhibitor and 5- HT1a partial agonist (has effects on glutamate system)
- Vortioxitene **(Brintellix)** – 5-HT reuptake inhibitor, agonist at 5-HT3, 5-HT-7, 5-HT1B (NE, DA, glutamate, histamine effects)
- Levomilnacipran **(Fetzima)** – 5-HT and NE reuptake inhibitor

Ketamine: A New Drug for Depression?

- A complex drug with effects on the NMDA receptor, opiate receptors, and reuptake inhibition on serotonin, norepinephrine,and dopamine.
- It also has a high potential for abuse.
- Currently is administered intravenously, usually in pain clinics, and generally has short-term effects. May be particularly useful in emergency management of suicidal ideation and behavior.

(Reminder)
How do the Neurons Communicate?



- Chemical Signals
- Electrical Signals

They each cause the other to respond

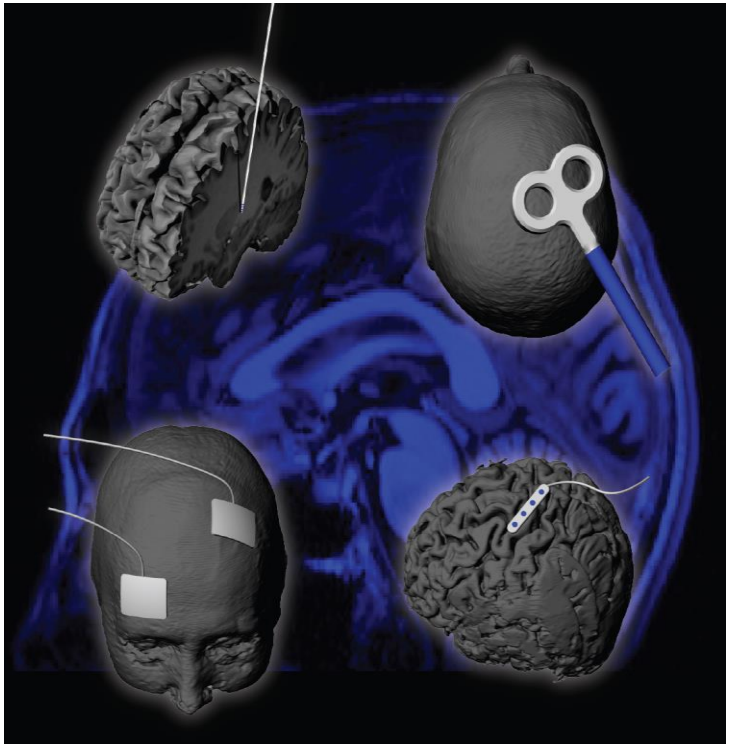
Neuromodulation – Old and New

Electroconvulsive Therapy

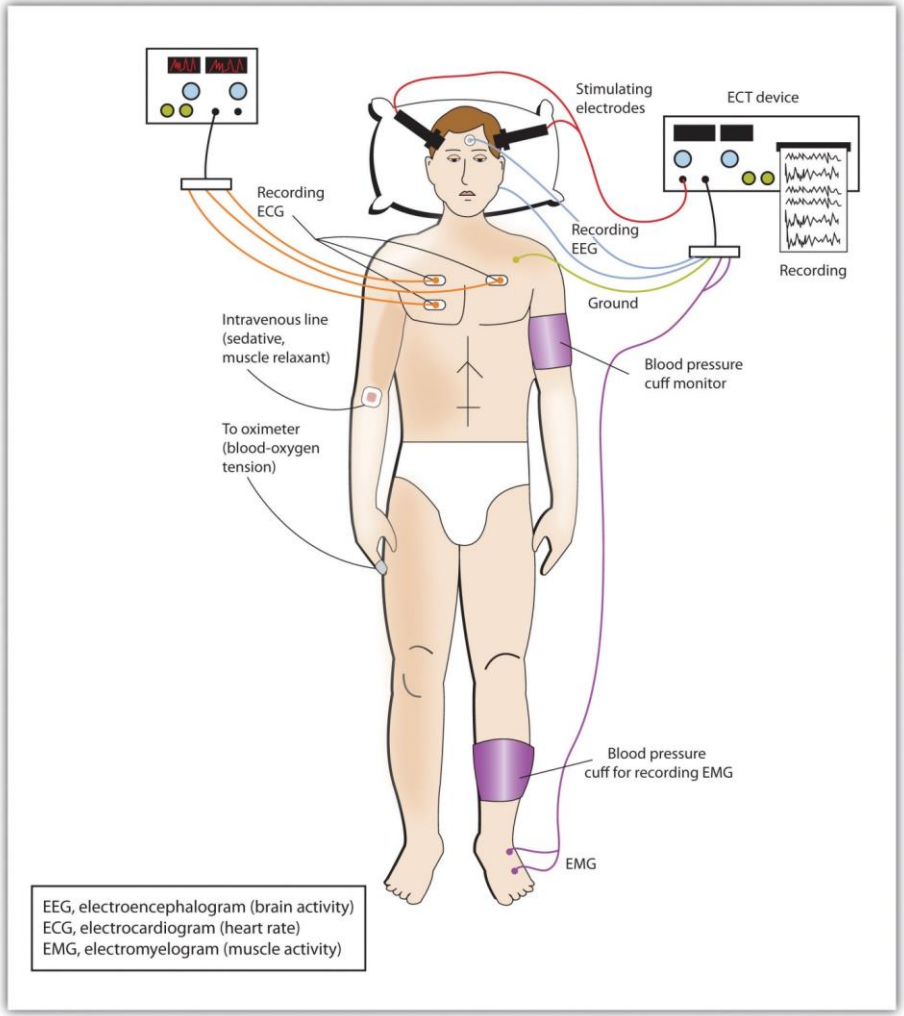
Vagal Nerve Stimulation

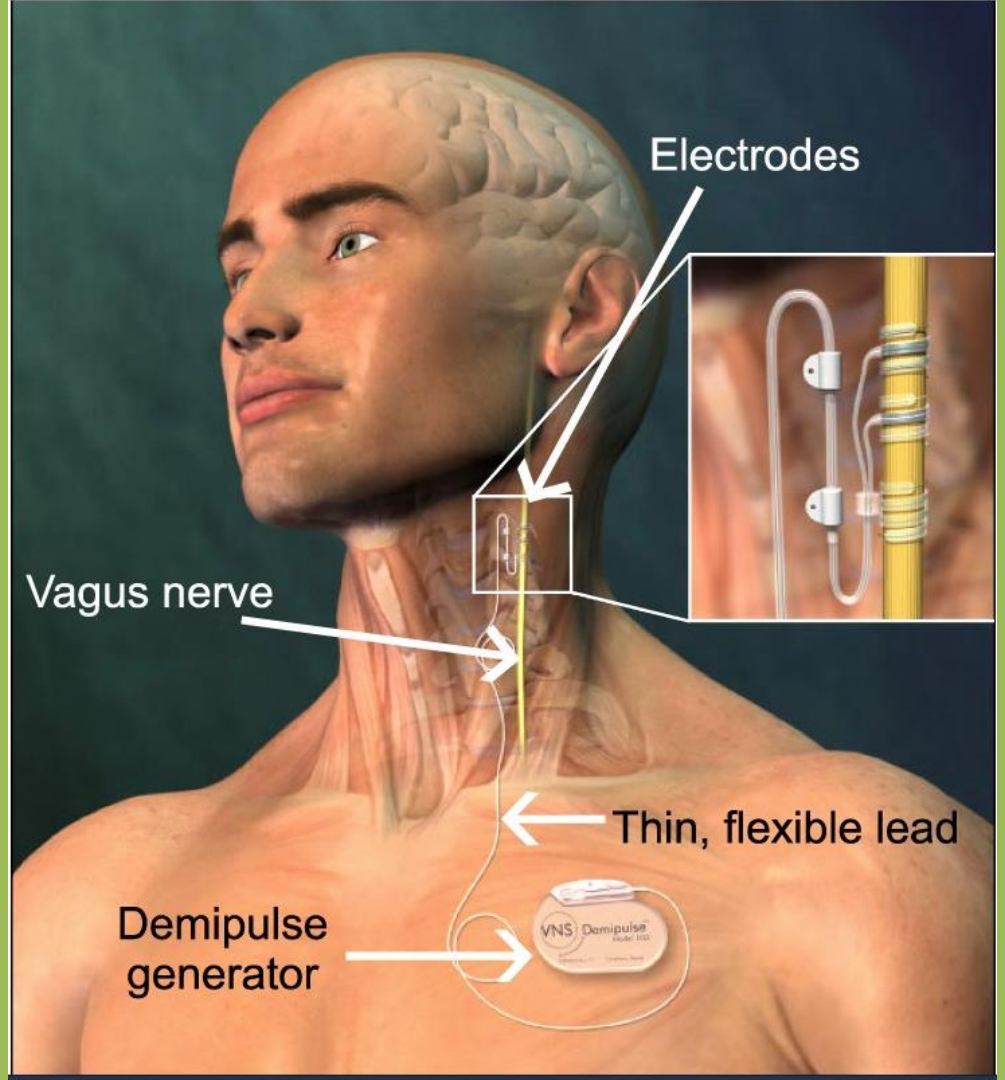
Deep Brain Stimulation

Transcranial Magnetic Stimulation

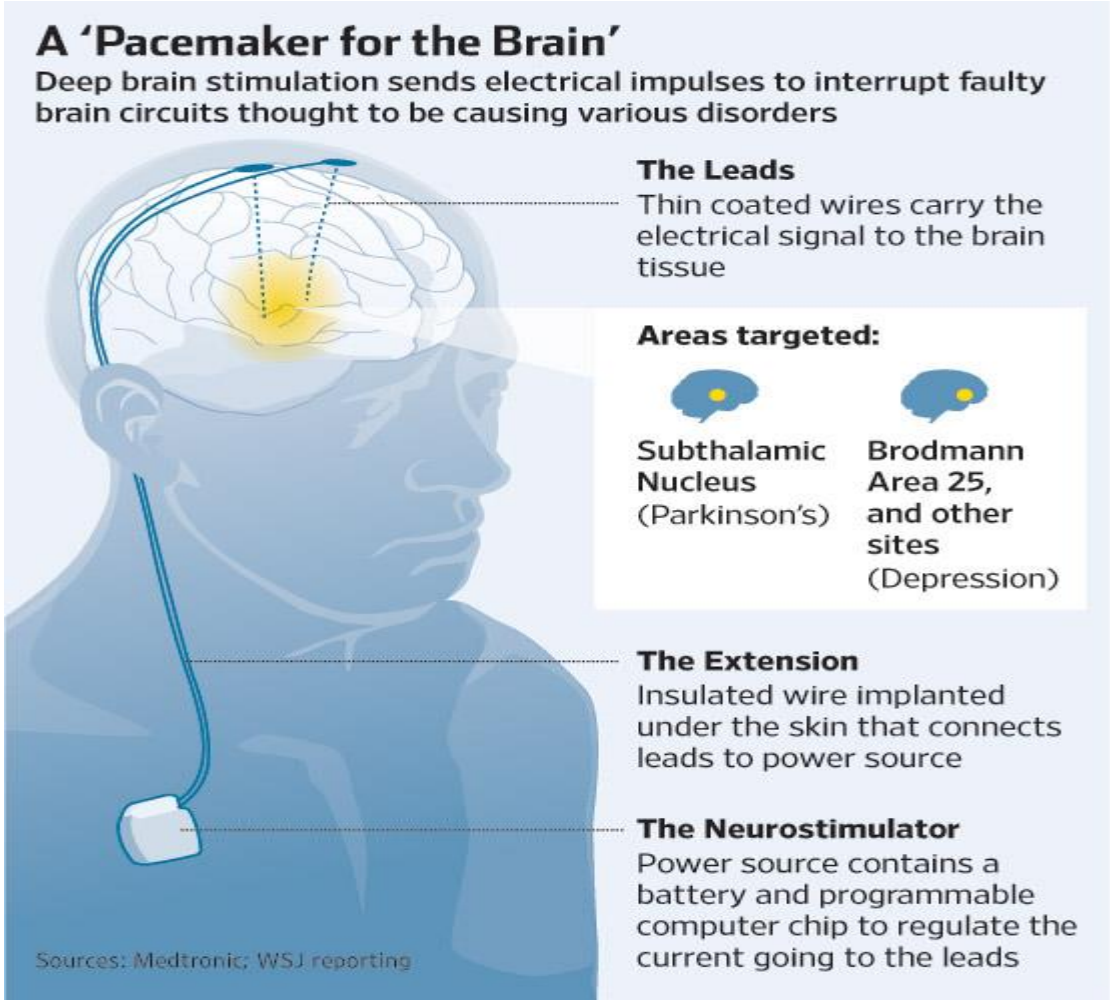


ECT:
Electroconvulsive Therapy



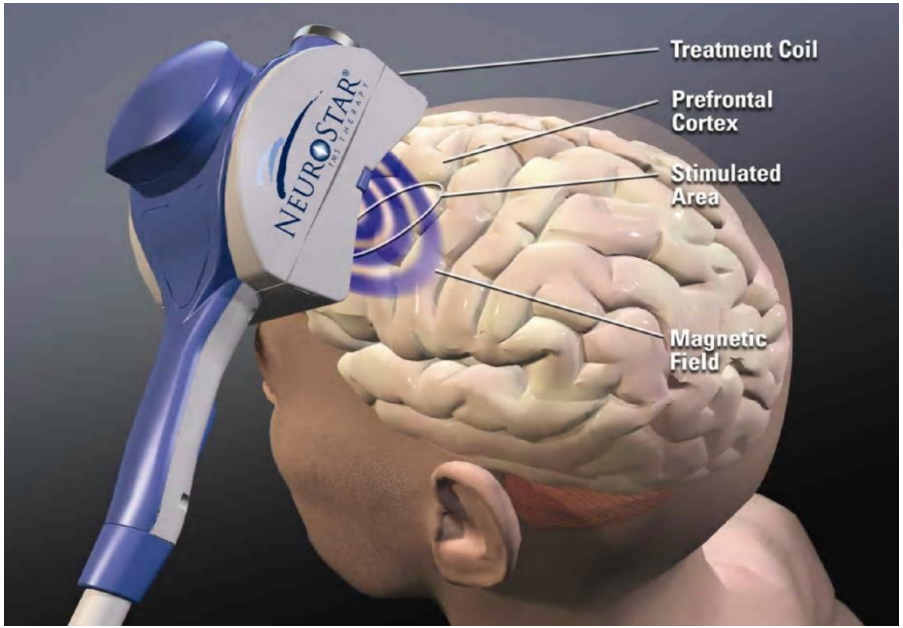

Electrodes
Vagus nerve
Thin, flexible lead
Demipulse generator
VNS Demipulse

DBS:
Deep Brain Stimulation



Transcranial Magnetic Stimulation (TMS)

- Application of electromagnetic induction described by Michael Faraday in 1839
  - Faraday's Law: a time-varying magnetic field induces an electric current that runs perpendicular to the time-varying motion of the magnetic field[1,2]
- Clinical application: Pulsed magnetic fields can induce electrical currents in brain tissues and neurons[3]

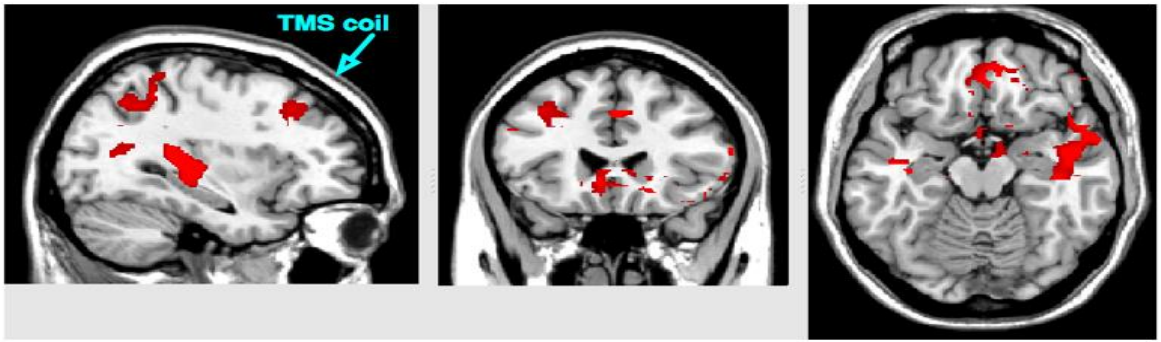


1. Faraday M. In: *Experimental Research in Electricity*. Vol 1. London Quaritch; 1839:1-15; 2. Barker AT. *J Clin Neurophysiol*. 1991;8(1):26-37; 3. Barker AT et al. *Lancet*. 1985;11(8437):1106-1107.

Biological Effects of TMS

Acute Effects

- Induces electric current
- Depolarizes neurons in superficial cortex
- Leads to local and trans-synaptic changes in brain activity



Example:

Left prefrontal TMS

23 depressed individuals

Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions

Li X et al. *Biol Psychiatry*. 2004;55(9):882-890; Teneback CC et al. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435; Epstein CM et al. *Neurology*. 1990;40(4):666-670.

NeuroStar TMS Therapy System

NeuroStar TMS Therapy System User Manual. Neuronetics, Inc: Malvern, PA; 2008.

TMS Therapy Session

- ~37 minute treatment
- Patient is awake and alert
    - no anesthesia or sedation needed
- No negative effects on thinking and memory
    - After treatment, patients can drive or return to work
- Some patients experience headache or mild to moderate pain or discomfort at or near the treatment area
- None of the side effects typical with antidepressant medications

Scientific Literature Supports the Antidepressant Effect of TMS

- More than 30 controlled clinical research studies
- Meta-analysis[1]:
  - 34 studies involving 1,383 patients
- 3 Randomized Sham Controlled Studies
    - 2 Corporate Sponsored
    - 1 Independent NIMH Study

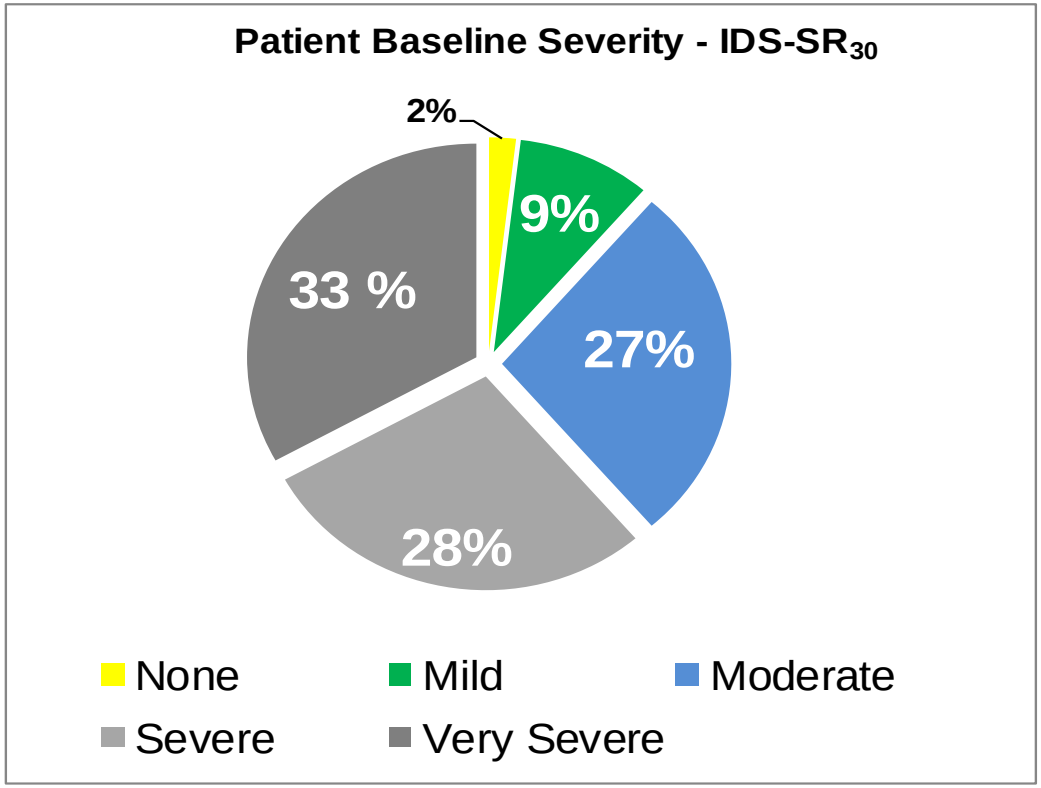
[1.] Slotema, et al. *J Clin Psych* (2010)

TMS Therapy Safety Summary Neuronetics Study

- Safety population (N=325)
  - Nearly 10,000 active treatments across all studies
- No seizures, no suicides, no deaths
- No systemic side effects such as weight gain, sexual dysfunction, nausea, dry mouth, sedation, or agitation
- Discontinuation due to adverse events <5%
- No adverse effect on cognition or auditory threshold
- Most common adverse events were headache and application site pain, which were transient and mild to moderate in severity

Austin TMS Clinic for Depression
Baseline Patient Characteristics
(N = 106)

Patient Characteristics N=106	
N(%) Females	56 (53%)
Mean Age (Years + SD)	53.0 ± 15.0
Age Range	22 - 78
Mean Failed Medication Trials	5.6 ± 3.3
Number of Failed Medication Range	1 - 16
% of Patients with Prior Hospitalization for Depression*	50%
% of Patients with Prior ECT TX for Depression*	7.30%
Baseline Symptoms Score	
IDS-SR_{30} Mean Score	42.5 ± 12.4



Average Medication Failures in Current Episode

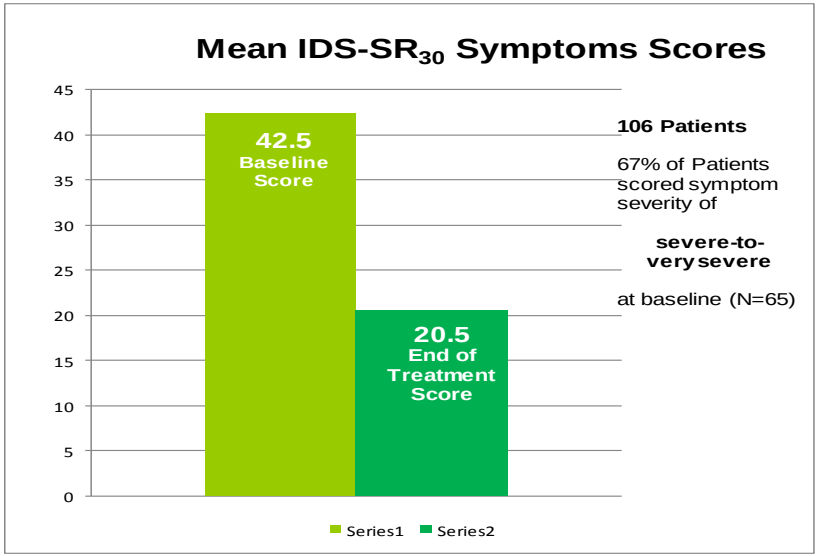
5.6 ±3.3
(Range 1-16)

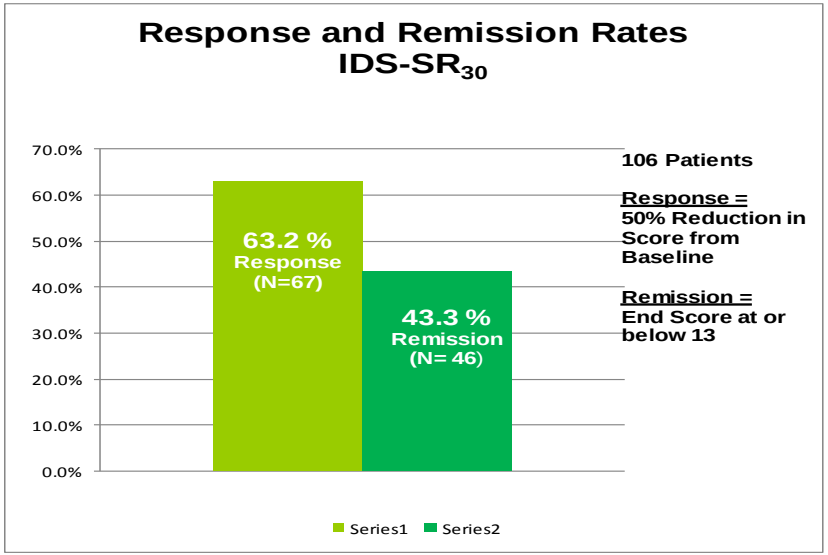
* Data presented at 2015 Clinical TMS Society, Toronto, Canada, May 2015

Austin TMS Clinic for Depression

TMS RESULTS

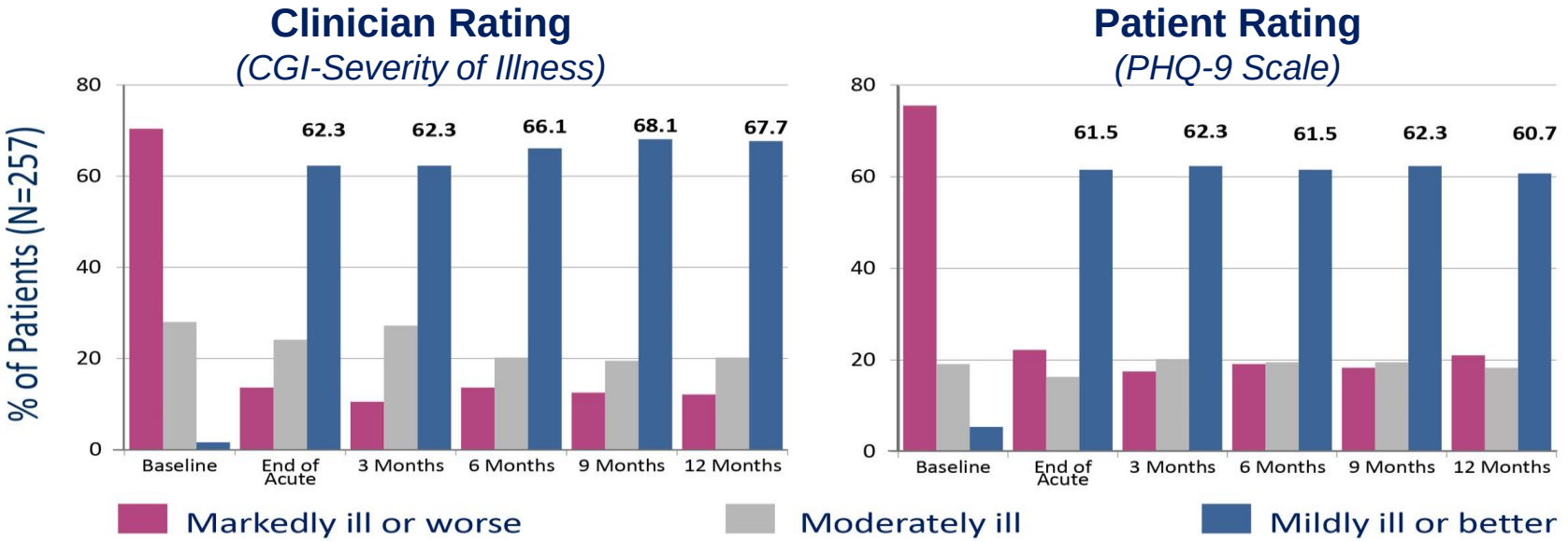
Complete Results Published at 2015 Clinical TMS Society Poster[1]





[1]Data on file

Long Term Results at 12 Months



LOCF Analysis of intent-to-treat population

Long term durability of effect has not been established in a controlled trial

. Dunner, et al., J Clin Psychiatry (2014).

NeuroStar TMS Therapy: Indication

"NeuroStar is indicated for the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from **one** prior antidepressant treatment at or above the minimal effective dose and duration in the current episode"*

*** In clinical trials, patients received a median of 4 treatment attempts, one of which was at adequate dose and duration.**

NeuroStar TMS Therapy System User Manual. Neuronetics, Inc: Malvern, PA; 2008.

Which Patients Can Benefit from TMS?

When Psychotherapy and

- Antidepressants are not working to provide FULL relief of symptoms
- If medications are causing side effects - limiting quality of life
  - Sexual dysfunction, Weight gain, Dry mouth, Confused thinking
- Pregnant or Breast Feeding
- Non-mental health medications that conflict with antidepressants

Who may not be eligible?

- May not be used in patients with implanted metallic devices or non-removable metallic objects in or around the head (excludes dental fillings).

- There may be other considerations – we can help assess these.

Agenda

Future Therapeutic Targets of Interest:

Anxiety, Including PTSD

Bipolar Disorder

Cognitive Dysfunction

Eating Disorders

Traumatic Brain Injury

Schizophrenia

Questions and Answers

Emilie Attwell Becker, M.D.
Mental Health Medical Director
Texas Medicaid and Chip Program
Texas Health & Human Services Commission

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For those in the auditorium, please come to the microphone to ask your question.

Sept. 23

Case Studies in Communications: An Insider's Guide for Tackling Topics, From Routine to Difficult

Presenters:
Melissa Loe, Communication Mgr., DSHS
Carrie Williams, Director of Media Relations, DSHS